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SYNTHETIC PORPHYRINS AND METALLOPORPHYRINS

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Synthetic Porphyrins and Metalloporphyrins

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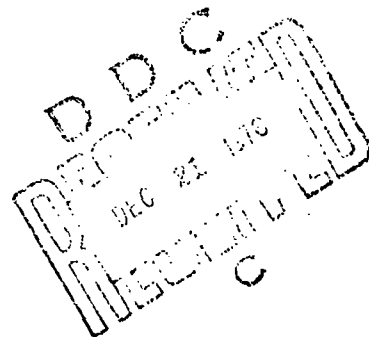
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## Synthetic Porphyrins and Metalloporphyrins

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The entire field of porphyrin chemistry has undergone rapid and dramatic changes in the last decade. One area of great importance involves "synthetic" porphyrins and metalloporphyrins.

Porphyrins are tetrapyrrole macrocycles formed by adding substituents to the nucleus of the parent compound porphine (Fig. 1).

Fig. 1

Naturally occurring porphyrins are generally found to have substituents in positions 1-8 and are named according to the number and type of substituents.<sup>1</sup> "Synthetic" porphyrins are those which are not found in nature but have been prepared in the laboratory by totally synthetic routes or by modifications of naturally occurring porphyrins. Figure 2 shows protoporphyrin IX, one of the most abundant "natural" porphyrins,

Fig. 2

and meso-tetraphenylporphine, a synthetic porphyrin often used as a model for naturally occurring porphyrins.

Replacement of the two pyrrole protons of a porphyrin by a metal ion leads to the formation of a metalloporphyrin (Fig. 3). Free base

Fig. 3

porphyrins are generally biologically unimportant, but metalloporphyrins are widely found in nature (some of the important biological porphyrin and porphyrin-like species are listed in Table I).

Table I

"Synthetic" metalloporphyrins are of two types: 1, synthetic porphyrins complexed with any metal ion, and 2, naturally occurring porphyrins complexed to metals other than those found in the naturally occurring metalloporphyrin.

Most metalloporphyrins exhibit square-planar coordination<sup>2,3</sup> with the metal ion sitting in the plane of the four porphinato nitrogen atoms. However, the porphyrin can also function as a bi-, tri- or hexadentate ligand, and the metal ion may possess 2-, 3-, 4-, 5-, 6- or 8-coordination. Like other macrocyclic ligands, porphyrins have a central hole whose size is essentially fixed. The size of the hole can be altered by puckering of the macrocycle, but this phenomenon is limited<sup>3</sup> and the range is generally observed to be between 1.93 and 2.05 Å. It is clear that in many complexes the metal ion is too large to fit inside the hole and will be forced to lie out of the plane of the macrocycle (Fig. 4).<sup>4</sup> Such out-of-plane complexes are of great interest

Fig. 4

because the unusual geometry may affect chemical reactivity. For example, the iron atom lies out of plane in deoxyhemoglobin while it is approximately in plane in the oxygenated form.<sup>4,5</sup> It is thought

that the transition between these states is responsible for the cooperative nature of oxygen binding in hemoglobin.<sup>6</sup>

Porphyrins and metalloporphyrins are of interest to disciplines ranging from biochemistry and medicine to industrial catalysts. Much of the interest arises from the relation of porphyrins to biological systems<sup>7</sup> and the use of metalloporphyrins as model compounds for such systems. These systems play a vital role in such processes as photosynthesis, enzyme catalysis, gas transport and electron-transport. Alterations in the metabolism of porphyrins have been associated with certain disease syndromes, drug metabolism and cancer. Porphyrins and metalloporphyrins such as tetraphenylporphine sulfonate and hematoporphyrin have been found to possess an affinity for cancerous tissue.<sup>8</sup> These finds suggest the clinical use of this type of material as diagnostic aids.<sup>9</sup> Other porphyrin and metalloporphyrin compounds have been used as curative agents or as precursors for new anticancer drugs.<sup>10</sup> Metalloporphyrins have also been reported to selectively stain elastic tissue<sup>11</sup> and may be used for this purpose in the laboratory. Metalloporphyrins may also be utilized in biological studies as labeling agents. This is demonstrated by the observation that cobaltohemoglobin, obtained by replacement of the iron in hemoglobin with  $\text{Co}^{\text{II}}$ , maintains reversible oxygen-carrying ability quantitatively similar to that of the original hemoglobin.<sup>12</sup>

Metalloporphyrins are being intensively studied for other than biological reasons. Some of the more important areas of interest

include the search for superconductors,<sup>13</sup> semiconductors,<sup>14</sup> improved catalysts for various industrial applications,<sup>15-18</sup> electrocatalysts (e.g. as fuel cell electrodes)<sup>19</sup> and as chemical shift reagents for nuclear magnetic resonance studies.<sup>20</sup> Phthalocyanines,<sup>21</sup> compounds closely related to porphyrins, have been widely used as dyes and as the green and blue colorings in banknotes and bonds. Studies have also been conducted on polymeric phthalocyanines and metallophthalocyanines<sup>22</sup> for possible use as pigments or as heterogeneous catalysts. The presence of metalloporphyrins in crude petroleum<sup>23,24</sup> necessitates care in the design of "cracking" catalysts.

However, even if there were no biological or industrial implications to porphyrins and metalloporphyrins, they would still be intensely investigated for their importance to modern theories of structure and bonding. In light of these implications, a knowledge of synthetic porphyrins and metalloporphyrins could be useful even to the non-specialist.

Porphyrin chemistry began<sup>25</sup> in 1880 with Hoppe-Seyler's isolation of hematoporphyrin (a "natural" metalloporphyrin). The first "synthetic" metalloporphyrins, mesoporphyrin IX complexes of Cu(II) and Zn(II) were prepared<sup>26</sup> in 1902. Research continued from these beginnings and much of our knowledge of the structure and chemistry of porphyrin compounds was gained in the first half of this century.<sup>27</sup>

As research continued and interest in porphyrins grew, Falk published an excellent review in 1964. Because of the explosive growth and heightened interest in the field, several more recent comprehensive

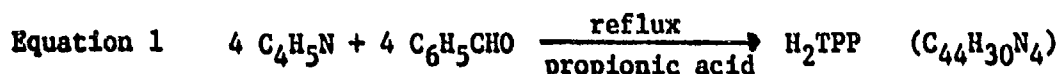


reviews of the area have appeared. These include reports of Symposia of the New York Academy of Sciences<sup>28</sup> and Smith's updated treatment of Falk's original volume.<sup>29</sup>

### Synthesis of Porphyrins

A variety of techniques are available<sup>29</sup> for preparation of both natural and synthetic porphyrins. Dipyrrole intermediates have been used extensively<sup>1,25,30</sup> in preparation of natural porphyrins, e.g. in deuteroporphyrin IX<sup>31</sup> and in Woodward's synthesis of chlorophyll.<sup>32</sup>

Synthetic porphyrins may be prepared by the cyclic condensation of monopyrroles with aldehydes.<sup>33</sup> An example of this method is the single-step preparation of the widely used meso-tetraphenylporphine<sup>34</sup> (Equation 1). Polymerization reactions are not always so simple, as



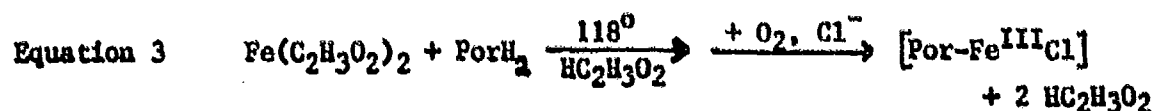
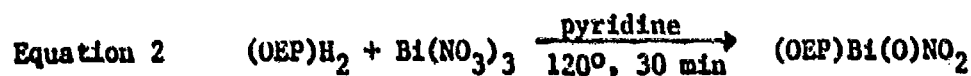
evidenced by the multi-step procedure required for the synthesis of octaethylporphine<sup>35</sup>.

Synthetic porphyrins may also be prepared from discrete open-chain tetrapyrrolic intermediates built up in a step-wise manner.<sup>29</sup> This method offers many possible procedures, but often yields a mixture of several different porphyrins from a single open-chain tetrapyrrole intermediate. Many porphyrins are currently prepared by this method. Mesoporphyrin IX dimethylester, a synthetic porphyrin which can be produced by chemical modification of a natural porphyrin, is synthesized by this method.<sup>36</sup>

In general, the last decade has provided dramatic approaches to the synthesis of porphyrins.<sup>37</sup> The early methods required harsh reaction conditions, while more recent approaches such as the use of open-chain tetrapyrroles involve milder conditions. Use of milder conditions allows labile or complex side-chains to be preserved intact during the reaction, permitting the synthesis of previously unknown or unattainable porphyrins.

#### Synthesis of Metalloporphyrins

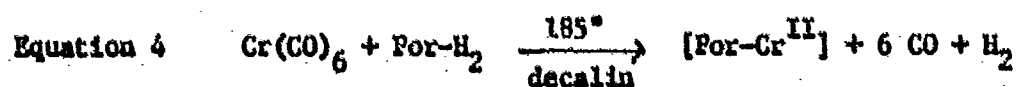
Metal complexes of natural porphyrins are commonly synthesized by combining a metallic salt and the free porphyrin in the same solution under reactive conditions. Synthetic metalloporphyrins can also be prepared in this manner. The reactions are generally carried out in a basic or acidic medium (e.g. pyridine<sup>38</sup> or acetic acid<sup>39</sup>).



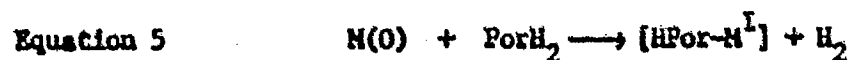
These methods are complicated by the fact that good solvents for the metal salts (as simple metal ions) are generally poor solvents toward the free (unionized) porphyrins. In basic reaction media, the porphyrin must compete with the solvent as a complexing agent toward the metal ion. Acidic media usually require a very large excess of the metal ion to drive the metal insertion reaction to completion, especially with porphyrins which readily form the porphyrin

di-acid cation,  $\text{Por-H}_4^{2+}$  or in cases in which the resulting metalloporphyrin has a low degree of thermodynamic stability, e.g.  $\text{Zn}^{+2}$  complexes. Other problems encountered in metalloporphyrin synthesis include those caused by the stability of the metal carrier, e.g.  $\text{MX}_3\text{L}_3$ , lability of the metalloporphyrin product under reaction conditions and the difficulty of preserving complex or labile side-chains during the synthesis. Many of these serious drawbacks to metalloporphyrin synthesis have been largely circumvented in the last decade by the development of new synthetic techniques.

The first new synthetic technique to be discovered utilized a carbonyl complex as the source of the metal to be inserted.<sup>40,41</sup> In this method, the porphyrin is oxidized by the reduction of the pyrrole protons of the porphyrin; earlier methods involve a simple ligand exchange with the porphyrin dianion. An example of this method is given in Eqn. 4, where  $\text{Por}$  = porphyrin dianion. Although there have been no detailed mechanistic studies of this class of re-

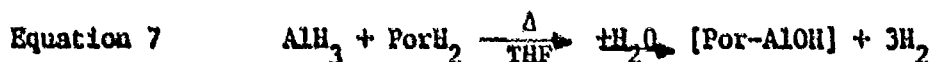


actions, it is probable that the metal insertion reaction is driven toward completion by the evolution of carbon monoxide and hydrogen. The metal may be oxidized in a series of one electron steps accompanied by a series of one electron reductions of the pyrrole protons.

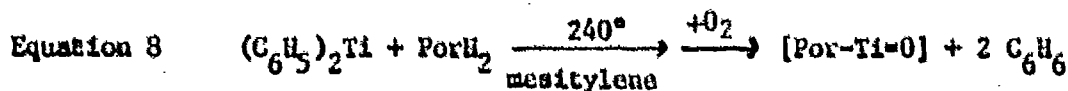


The carbonyl method has been used to synthesize previously unknown complexes of chromium,<sup>41</sup> molybdenum,<sup>42</sup> ruthenium,<sup>43,44</sup> rhodium,<sup>45</sup> iridium,<sup>46</sup> rhenium,<sup>47</sup> and technetium.<sup>48</sup> Other methods have subsequently been used to prepare complexes containing some of these metals, but the metalloporphyrins prepared by the carbonyl method are still unique. Metalloporphyrins obtained by the carbonyl method may possess one or more carbonyl ligands bound to the metal which is often in a low oxidation state. An example of this type of complex is the rhodium (I) complex  $\text{OEP}[\text{Rh}(\text{CO})_2]_2$ .<sup>49</sup>

Related synthetic techniques involve the use of a metal hydride complex or an organometallic compound as the metal source. The metal hydride method involves the oxidation of hydride ions<sup>50</sup> (e.g. equation 7), but is limited by the small number of metals for which hydrides



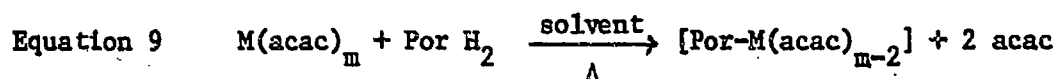
are available. Diphenyltitanium has been used to prepare a titanyl complex with mesoporphyrin IX dimethylester<sup>51</sup> (Eqn. 8).



The titanium is oxidized to the +4 state by air during the reaction. The use of organometallics is one of the most powerful methods available for a metal insertion process, and has been used to prepare methylmercury derivatives of porphyrins.<sup>52</sup> However, the availability of other synthetic methods and the inconvenience involved in working with organometallic derivatives have served to limit the use of

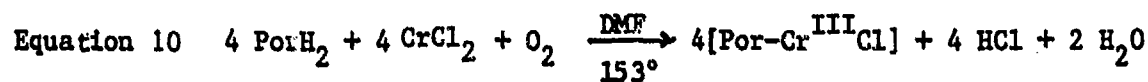
this technique.

A synthetic technique developed by Buchler and co-workers<sup>53</sup> utilizes metal acetylacetonates as a source of metal ions. The acac complexes are readily available and reasonably soluble in organic solvents. Investigations were carried out on the reaction of octaethylporphine with metal acetylacetonates in molten phenol, quinoline and imidazole (Eqn 9). A number of previously known metalloporphyrins as well as new complexes of zirconium (IV)<sup>53</sup> and hafnium(IV)<sup>54,55</sup> were



prepared by this method. The method has recently been used to prepare complexes of homoporphyrins<sup>56</sup> - porphyrins possessing a two-carbon meso bridge between two pyrrole rings.

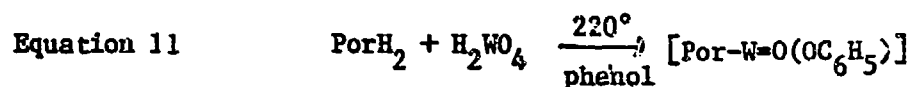
Adler and coworkers<sup>57</sup> overcame the metal solubility problem by using N,N-dimethylformamide (DMF) as a solvent. The porphyrins are soluble in the organic medium while the highly polar nature of the solvent increases the solubility of the metal salts. Application of this method led to improved yields of many known compounds and to the synthesis of new compounds. One notable success of this method was the preparation of the once-elusive chromium porphyrin (Eqn. 10).



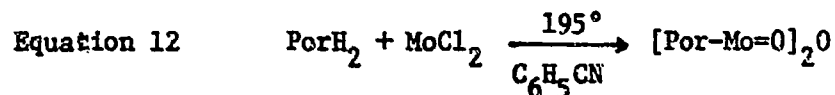
Today this method is used to prepare a variety of metalloporphyrins and porphyrin-like metal complexes.<sup>58</sup> Polar media had previously been used, but the lower dielectric constants of solvents such as

acetone, dioxane and ethanol<sup>59</sup> make them less useful than DMF.

The use of media having high dielectric constants in metalloporphyrin synthesis was further explored by Buchler.<sup>54</sup> He successfully prepared complexes of scandium, tantalum, tungsten, osmium and rhenium using metal halides or oxides in a phenol melt (Eqn. 11).



The use of benzonitrile led to many novel complexes, including those of chromium, molybdenum, tungsten and niobium (Eqn. 12). The preparation



of the tungsten complex is of interest since attempts to prepare similar materials utilizing tungsten hexacarbonyl had proved unsuccessful.<sup>60</sup>

The development of these new synthetic methods has made possible the synthesis of many metalloporphyrins which were previously unknown. Many of the complexes contain labile groups in axial positions which serve as a key to the kinetics and mechanisms of these species both as coordination compounds and as biological models. At least one porphyrin complex is known for virtually every metallic element, and new compounds are being prepared continually. While all porphyrins and metalloporphyrins of potential interest are obviously not known, one can state that the preparation of any reasonable porphyrin complex desired should be attainable through these new and powerful syn-

thetic techniques.

### Structure of Metalloporphyrins

The definitive method of structural determination of metalloporphyrins is single-crystal X-ray diffraction. Other less rigorous but nevertheless useful methods of assigning structures to these species include NMR, IR, UV and visible spectroscopy. X-ray diffraction studies have received serious attention in recent years beginning in the period 1962-1965.<sup>61</sup> Since that time, much has been learned about the various structural characteristics of porphyrins and metalloporphyrins. The major structural classifications of metalloporphyrins is based on whether the metal lies in or out of a plane defined by the porphyrin molecule. These "in-plane" and "out-of-plane" groupings can be further divided by considering the presence and nature of axial ligands and by the number of metal atoms contained in the metalloporphyrin.

In-plane, monometallic species may exhibit varying coordination numbers, but the most common (and best characterized) values are 4 and 6. These complexes are typified by octaethylporphinetonickel(II),<sup>62,63</sup> Ni(OEP), tetraphenylporphinatoiron(II),<sup>64</sup> Fe(TPP), dichlorotetraphenylporphinatotin (IV)<sup>65</sup> (Cl)<sub>2</sub>Sn(TPP), (Fig. 5), bis(imidazole)-tetraphenylporphinatoiron (III) chloride,<sup>66</sup> [(Im)<sub>2</sub>Fe(TPP)]Cl and dichlorooctaethylporphinatotin (IV) nitromethane solvate,<sup>67</sup> (Cl)<sub>2</sub>Sn(OEP) · 2 CH<sub>3</sub>NO<sub>3</sub>.

Fig. 5

The first and last species are of particular interest because they represent the smallest [ Ni(II) ] and largest [ Sn(IV) ] metal atoms that have been shown to be centered in the "hole" of the porphyrin moiety. Tetragonal crystals of  $(\text{Cl})_2\text{Sn}(\text{TPP})$  contain the metal in the center of a completely planar porphyrin core. However, metalloporphyrins are known in which the metal atom lies in the center of the porphyrin, but the porphyrin itself is "puckered" or "ruffled" instead of planar. This distortion of the ring to accommodate the metal atom can be slight as in the case of  $\text{Ni}(2,4\text{-Diac Deut-IX-DME})^{68}$  or extreme as in  $\text{Cu}(\text{TPP})$  and  $\text{Pd}(\text{TPP})$ ,<sup>69</sup> both of which contain the porphyrin in a strongly ruffled conformation.

Out-of-plane monometallic complexes have been described in terms of the two models shown in Fig. 4 & 6. Hard<sup>4</sup> proposed a square pyramidal

Fig. 6

complex as the intermediate in the hemoglobin oxygen transport mechanism. Fleisher<sup>71</sup> proposed a "sitting atop" (SAT) complex as the intermediate in the metal insertion mechanism. In this configuration, (SAT), the porphyrin is deformed to facilitate deprotonation and subsequent incorporation of another metal atom into the porphyrin core from the opposite side. Examples of this type of complex are zirconium-(IV)<sup>53</sup> (Fig. 7) and Hf(IV)<sup>54,55</sup> which form stable, out-of-plane monometallic

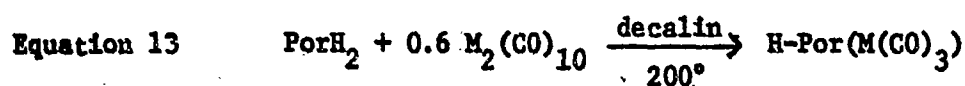
Fig. 7



porphyrin complexes each containing two bidentate acetate ligands.

X-Ray analysis<sup>71</sup> has confirmed this proposed structure with the metal atom out-of-plane, but lying on the  $S_2$  axis normal to the porphyrin as required in both models.

A new type of monometallic out-of-plane complex has been prepared<sup>72</sup> (Eqn. 13) where  $M = \text{Re, Tc}$  and  $\text{Por} = \text{H-MP, H-TPP, H-OEP}$ . The



metal atom lies out of the porphyrin plane, but in contrast to the two models, it lies off the  $S_2$  axis normal to the plane of the porphyrin (Fig. 8). Variable-temperature nmr studies indicate dynamic

Fig. 8

intramolecular fluxional behavior<sup>73</sup> involving migration of the metal atoms about the face of the porphyrin ring. While dynamic fluxional behavior by coordinated ligands has been observed previously, this appears to be the first example of dynamic fluxional behavior by the metal atom in a metalloporphyrin complex.

Another type of out-of-plane complex is typified by the  $(\text{Cl})\text{Fe}(\text{TPP})$  species.<sup>74</sup> In this type of 5-coordinate complex, the metal atom is centered on the  $S_2$  axis, but is out of the plane of the ring. This vertical displacement above the ring is strongly dependent on both the nature (and size) of the metal and on the nature of the axial ligand. The displacement ranges from a few hundredths of an Angstrom (in the

(Cl)Fc(TPP) case) to several tenths of an Angstrom.

Porphyrin acid species which do not contain metal ions also exhibit interesting variations in structure. Determination of the structures<sup>3,75</sup> of  $H_4(TPP)^{2+}$  and  $H_4(TPyP)^{2+}$  reveal a tilting of the ring toward a disphenoidal (dished) geometry with the pyrrole rings tilted from coplanarity by at least  $25^\circ$ . This may be contrasted to  $[H_4(OEP)]^{2+}$   $[Rh(Cl)_2(CO)]_2^{76}$  in which the cation maintains a nearly planar conformation. The monoprotinated species  $H_3(OEP)^+I_3^-$  has been observed<sup>77</sup> to have 3 pyrrole rings coplanar (within 0.03 Å) and the fourth ring inclined by  $14^\circ$ . Two other monoprotinated species,  $H_3(OEP)^+[Re_2(CO)_6Cl_3]^-$  and  $(H_3MPiXDME)^+[Re_2(CO)_6Br_3]^-$  have been recently prepared and their structures are being investigated.<sup>78</sup> Preliminary results indicate the two cations have the same structure, with three rings nearly planar and one tilted.

Bridged metalloporphyrins are of interest as model compounds for electron transfer, and a number of types of bridged and metal-metal bonded complexes are known. The nitrogen-bridged polymeric system  $[Fe(TPP)(imidzolate)]_n$  (Fig. 9) exhibits<sup>79</sup> spin-coupling through the

Fig. 9

imidazoles, demonstrating the ability of the ligand to function as an electron bridge when coordinated to an iron porphyrin. Another interesting complex is a trimeric system involving two iron (III) porphyrin azides and an iron (II) porphyrin.<sup>80</sup> Magnetic studies show the presence of four unpaired electrons and suggest the existence of a

single orbital extending the length of the molecule interconnecting all three iron atoms.

Oxygen bridges have also been intensively investigated. An important example is the oxo-bridged "hematin" dimer (Fig. 10). This

Fig. 10

complex was long thought to be a mononuclear hydroxide and has only recently been recognized as a dinuclear, out-of-plane complex.<sup>81</sup> The ability of this oxo-bridge to conduct electrons is clearly demonstrated by strong antiferromagnetic coupling between the iron atoms. Oxygen-bridged dimers have been prepared for porphyrin complexes of other metals<sup>54</sup> such as aluminum (III), scandium (III), and niobium (V), molybdenum (V), tungsten (V), and rhenium (V). The last four complexes have been shown to contain two M=O groups in the plane of the porphyrins linked by an oxygen bridge (Fig. 11).

Fig. 11

Halide bridging species have been proposed as intermediates and identified spectroscopically, but to date have not been completely characterized. A dinuclear "sitting-atop" complex (Fig. 12) has been

Fig. 12

proposed<sup>82</sup> as an intermediate in the reaction of  $\text{FeCl}_3$  with  $\text{H}_2$ -(proto-

IX-DME) (protoporphyrin IX dimethyl ester).

Metalloporphyrins containing metal-metal bonds have been identified. Metal-metal interactions have been observed in the solid state for chromium(II)mesoporphyrin-IX dimethylester.<sup>40</sup> The product of the photochemical dimerization of a ruthenium porphyrin(Fig.13) has been reported<sup>83</sup>

Fig. 13

to exhibit some type of metal-metal interaction. Metal-metal interactions have also been observed in the solid state for chromium (II) mesoporphyrin-IX dimethyl ester.<sup>40</sup> The existence of Zn-Zn bonds is strongly suggested by studies<sup>84</sup> of  $(\text{Zn}(\text{OEP})\text{Br})_2$  and  $(\text{Zn}(\text{Pc})\text{Cl})_2$  [Pc=phthalocyanine]. This proposed dimeric structure (similar to Fig. 13 with a halogen bonded to each Zn) can be obtained only when the porphyrins has no bulky substituents and the rings can parallel each other and allow electron coupling through the  $\pi$  clouds.

Another major type of out-of-plane metalloporphyrin is the polymetallic complex. Hambright<sup>85</sup> has proposed a dimetallic monoporphyrin complex (Fig. 14)

Fig. 14

as an intermediate in metal-insertion reactions. In this model the metal atoms lie above and below the porphyrins on the  $S_2$  axis perpendicular to the plane (a "double-barreled" "sitting-atop" model). Tsutsui and co-workers have synthesized the dimetallic complexes of rhenium<sup>46,72</sup> and technetium<sup>47,48</sup> and the mixed Re, Tc species.<sup>86</sup> X-Ray diffraction analysis<sup>43,46</sup> (Fig. 15)

Fig. 15

show the metal atoms lie above and below the porphyrin, but unlike Hambright's model, they lie off the  $S_2$  axis. The distance between the metals is too long for a formal bond ( $3.114 \pm 0.013 \text{ \AA}$ ) but short enough to permit some metal-metal interaction, and the porphyrin ring is highly distorted. In these complexes, each metal achieves pseudo-octahedral coordination by coordinating to three of the four pyrrole nitrogens as was found in the monometallic species.

A related compound,  $[(\text{OEP}) \text{Rh}(\text{CO})_2]_2$  (Fig. 16) has been found<sup>87</sup>

Fig. 16

to have rhodium ions above and below the plane of the porphyrin. Each rhodium possesses square-planar symmetry and is bonded to two adjacent pyrrole nitrogens.

It should be noted that these metal carbonyl complexes differ from most porphyrin complexes in that the metal atoms are coordinated to 2 or 3 instead of all four pyrrole nitrogens. Thus it would appear that the carbonyl complexes having the metal in a low oxidation state preferentially coordinate adjacent nitrogen atoms (Fig. 17) instead

Fig. 17

of alternate nitrogens as in Hambright's model. Whether this model is valid for ligands other than carbonyl is unknown at this time.

A trimetallic mercury complex<sup>88</sup> (Fig. 18) (a "triple-decker" species)

Fig. 18

has recently been prepared. This compound suggests the possibility of forming extensive stacked polymers which might contain metal-metal bonds. Ionic type complexes (e.g.  $\text{Ag}^+$ ,  $\text{Hg}^+$ , etc.) would be likely to assume the structure shown in Fig. 18, while the more covalent-bonded complexes (e.g. Re, Rh, etc.) could form polymers as represented by Fig. 19. The presence of the large rings, delocalized electrons and

Fig. 19

the possibility of metal-metal interactions should make the stacked polynuclear metalloporphyrins good candidates for improved conducting materials.

#### Miscellaneous Structures

There are certain types of porphyrins and metalloporphyrins which do not fit neatly into any of the categories previously described, yet merit some attention. The first of these are the "peripheral complexes" in which the metal, instead of being bound to the inner nitrogens, is associated with substituents on the periphery of the macrocycle. An example of this type of species is the complex<sup>89</sup> formed between  $\text{Zn}(\text{TPP})$  and  $\text{Cr}(\text{CO})_3$ , (Fig. 20), in which the tricarbonylchromium (0) groups are

Fig. 20

$\pi$ -bonded to the phenyl rings. Another peripheral complex related to the chlorophylls has been investigated<sup>90</sup> by our methods. In this compound (Fig. 21),  $\text{Mg}^{++}$  is chelated by a  $\beta$ -ketoester function that is

Fig. 21

coplanar with the macrocycle.

A second type of unusual complex is the porphyrin-containing polymeric species. Compounds of this type are of special interest as semiconductors, heterogeneous catalysts and enzyme models. Wang<sup>18</sup> has prepared a polymer in which a heme group is bonded to a polystyrene-embedded imidazole derivative through the iron atoms. Polyporphyrins and polymer-attached porphyrins have also been prepared.<sup>17</sup> By using fixed-pore or macroreticular resins as anchors for porphyrins, one can obtain very porous materials which contain highly dispersed porphyrins. These porphyrins can then undergo metal insertion reactions and form highly dispersed, insoluble but accessible metalloporphyrin species (Fig. 22) suited for heterogeneous catalysis applications.

Fig. 22

The last type of complexes to be considered are the sterically hindered macrocycles. Examples of this class of complexes are the "capped" or "crown heme" species and the "picket-fence" porphyrins. These compounds are of particular interest as O<sub>2</sub>-carrier models. The "myoglobin model"<sup>91</sup> (Fig. 23) suggests the usefulness of this type of

Fig. 23

complex in either promoting or inhibiting reaction of a metal in the

core of a porphyrin macrocycle. Capped, or "crown heme" (due to the resemblance to crown ethers) porphyrins have been prepared (Fig. 24) and successfully metallated<sup>92</sup> with iron (III) and reduced to ferrous iron.

Fig. 24

This species was found to bind oxygen reversibly, with a lifetime of about 20 hours.

Collman has prepared<sup>93</sup> a macrocycle bearing four pivaloylamide residues. These residues have their steric bulk on one side of the porphyrin plane (Fig. 25) and the resulting compound is called a "picket-

Fig. 25

fence" porphyrin.

Iron derivatives of this porphyrin have been prepared and found to reversibly bind oxygen at room temperature and form a crystalline complex.<sup>94</sup> This behavior contrasts with the behavior of sterically unhindered iron (II) porphyrins which are reversibly oxidized only at low temperatures.<sup>95</sup> Structural determination of the  $(O_2)Fe(1-MeIM)(TpivPP)$ <sup>93</sup> and  $(OC)-Fe(1-MeIM)(TpivalPP)$ <sup>96</sup> show the imidazole to lie below the porphyrin plane while the  $O_2$  (or CO) is "inside the fence" and bent for  $O_2$  ( $\angle FeOO \sim 135^\circ$ ); linear for CO.

#### Implications/Properties/Uses

Some practical uses of porphyrins and metalloporphyrins have been



previously suggested. In light of the varied nature and properties we have discussed, it seems worthwhile to investigate more of the implications and applications of porphyrin complexes in several areas.

NMR studies of porphyrin and metalloporphyrins have dealt with the nature of hyperfine shifting of both  $^1\text{H}$  and  $^{13}\text{C}$  resonances and their interpretation in terms of porphyrin structure in solution and the nature of structure - function relationships. Perutz<sup>97</sup> has demonstrated the use of the nmr method as a tool for hemoprotein studies. Recently, metalloporphyrins have been utilized as induced-shift reagents (PIS) to complement lanthanide-induced shift (LIS) reagents.<sup>19,98,99</sup> Several compounds which show both ring-current and additional pseudo-contact shifts have been examined by Kenney<sup>19</sup> and co-workers. They have found the group IV metalloporphyrins, phthalocyanines and corresponding  $\text{Ru}^{\text{II}}$  and  $\text{Re}^{\text{II}}$  complexes induce smaller shifts than the lanthanides (about 8 ppm vs 25 ppm) but the PIS reagents are more stable and demonstrate greater selectivity.  $\text{Co}(\text{II})$  porphyrins have also been employed as pseudo-contact shift reagents by Hill.<sup>99</sup> Iron porphyrins and related compounds are of great interest because of their relation to hemoproteins and have been extensively investigated<sup>97,100</sup> in both equilibrium and kinetic studies. Undoubtedly this area will continue to be of great interest in both theoretical and experimental studies.

Porphyrins and metalloporphyrins hold great promise in the field of cancer as both diagnostic and curative aids. Sulfonated tetraphenylporphyrins and other species have been shown<sup>8</sup> to be localized in cancerous tissues. It may be possible to use these or related materials as diagnostic aids or as heavy-metal carriers to preferentially deliver metals

or alkylating materials to a cancer site thereby reducing or eliminating many of the side effects associated with drugs currently in use. Porphyrins have also been investigated as precursors for drugs which have demonstrated outstanding promise in treatment of certain types of cancer. As research continues in this field, medicine may well gain extremely powerful weapons for use in the fight against this dread disease.

The search for new catalytic materials is expanding to include the metalloporphyrins and many materials have demonstrated catalytic activity. Porphyrins (especially tetraphenylporphyrins) and phthalocyanines are particularly good candidates for heterogeneous catalysts for several reasons. They readily form metal complexes which are relatively thermostable. Many of the complexes are square-planar which leaves two sites (the axial positions) open for additional coordination. The  $\pi$ -system of the macrocycle may be modified by adding substituents which contribute or withdraw electrons from the system. Finally, many of the complexes can be dissolved in organic solvents, making it possible to study the properties of the metal more conveniently than if it were dispersed in the solid state in an active catalyst.

An example of a metalloporphyrin-catalyzed reaction is the oxidative dehydrogenation of cyclohexadiene (to benzene) by nitrobenzenes on Co(II) and Zn tetraphenylporphyrins and phthalocyanines.<sup>101</sup> These complexes also exhibit a photocatalytic effect which is most prominent for the Zn complexes. Since Zn(II) is isoelectronic with  $Mg^{2+}$  and chlorophyll (an active photocatalyst in nature) contains a  $Mg^{+2}$  ion in a porphyrin-like core, it has thus been possible to investigate simple model systems closely related to biological systems.

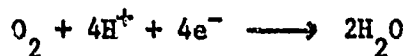
The advantage of being able to "tailor" the electronic effects of

the macrocycle on the catalyst has been demonstrated by showing an activity increase from zero for CoPc to trace activity for Co-tetrafluoro Pc to 50% conversion for Co-hexadecafluoro Pc.<sup>102</sup> Similar effects can be shown for porphyrin catalysts depending on the nature of substituent groups on the peripheral phenyl groups.

Porous, polymer-bonded metalloporphyrins have demonstrated catalytic activity for the oxidation of thiols to disulfides.<sup>17</sup> This type of reaction is of interest in the petroleum industry since it is related to the removal of mercaptan sulfur compounds from cracked gasolines and other products. In addition, the presence of natural porphyrins and metalloporphyrins in petroleum<sup>23,24</sup> leads to contamination and deactivation of cracking catalysts.<sup>103</sup> Significant progress in this area could constitute a major advance in light of the current world concern over energy by permitting the utilization of presently undesirable petroleum sources of high sulfur content.

Metalloporphyrin complexes are also being studied as catalysts for the direct combustion of fuels, converting combustion energy directly into electrical energy (i.e. fuel cells).<sup>19</sup> In this process, fuel is oxidized at the anode, and molecular oxygen is reduced at the cathode (Eqn. 14). This process is carried on very readily in the metabolic

Equation 14



mechanism of living organisms. However, nature does a much more efficient job and man-made catalysts fall far short of their accomplishments. Initial studies of catalytic electrochemical reduction of oxygen involved CoPc and acetylene black.<sup>104</sup> The material was an effective

catalyst, but inferior to Pt or Ag on carbon black. Studies of this type have continued and definite progress is being made in this area.<sup>19</sup>

Naturally occurring nitrogenase enzymes are involved in the fixation of nitrogen ( $N_2 \rightarrow NH_3$ ). Metalloporphyrins have been investigated<sup>105</sup> as possible models for these enzymes.  $Co(III)TPPS_4$  and borohydride in aqueous solution were found to reduce typical nitrogenase substrates in a two-electron transfer, producing ammonia in which the nitrogen atom did not come from the porphyrin. Further studies<sup>106</sup> have cast doubt on this observation and conclude that while  $NH_3$  is produced, the source of N was either the porphyrin itself or nitrogen-containing impurities in the air.

Despite the disappointing results obtained to date in nitrogen fixation, the value of metalloporphyrins as catalysts in such processes as olefin hydrogenation, the Fischer-Tropsch synthesis and other related areas is obvious.

The area of metalloporphyrin chemistry of greatest interest to many scientists is the use of these compounds as  $O_2$ -carrier models. Research ranges from very simplistic model systems to highly complex models of naturally occurring porphyrin-related systems. It is hoped that information gained by studying electron-transfer of metalloporphyrins may lead to an understanding of the hemoproteins and their redox behavior.<sup>107</sup> (Eqn. 15)

Equation 15  $M(III)Por + Reducing Agent \rightleftharpoons M(II)Por + Oxidizing Agent$

$(Py)_2Fe(II)Por$  will reduce  $O_2$  to  $H_2O$  in aqueous solution.<sup>108</sup> An important finding of this project was that charge separation of the type

$[\text{PorFe}^{3+} \dots \text{O}_2^-]$  was important; hence, the hydrophobic low dielectric cavity in which the iron atoms are found in hemoglobin and myoglobin would favor the "carrying" of oxygen rather than its reduction.

Mono-amine cobalt complexes  $[(\text{Por})\text{Co}(\text{II})-\text{L}]$  will react with molecular oxygen<sup>109</sup> and produce hydroxy monomers and binuclear peroxy adducts  $[\text{L}-(\text{Por})\text{Co}-\text{O}_2-\text{Co}(\text{Por})-\text{L}]$ . The reverse process (disproportionation of  $\text{H}_2\text{O}_2$  to  $\text{O}_2$  and  $\text{H}_2\text{O}$ ) is carried out in nature by the enzyme catalase. Cobalt and iron porphyrins<sup>110</sup> have been studied as possible models for this process. These systems provide a delocalized bridging system which promotes multiple electron transfers involving the coordinated oxygen species.

The oxygen molecule which is bound to a metalloporphyrin may have two orientations (Fig. 26). The specific orientation will affect both the

Fig. 26

activation of the dioxygen species and its interactions with substrates. The previously mentioned sterically hindered metalloporphyrins (generally containing iron) serve as model systems to study these interactions. Other simple oxygen-metalloporphyrin species have been investigated to determine the oxygen orientation. Oxotitaniumporphyrins ( $\text{PorTiO}$ ) have been prepared<sup>111</sup> for a variety of porphyrins. Treatment of oxotitanium-octaethylporphyrin ( $\text{OEP TiO}$ ) with benzoyl peroxide yields a peroxotitaniumporphyrin<sup>112</sup> in which the dioxygen is in orientation 1 (see Fig. 26). This is the first reported peroxometalloporphyrin in which the dioxygen is symmetrically bonded by both atoms and may serve to improve our understanding of the factors determining the nature of metal-oxygen

interactions in heme proteins.

The major biological role of heme proteins is the activation of molecular oxygen. This is accomplished by the donation of electrons from the iron  $\sigma$ -orbitals to antibonding  $\pi$ -orbitals of oxygen. Cytochrome P-450, a heme protein found in many living organisms<sup>113</sup> is an important biological mono-oxygenase. It is involved in the hydroxylation of metabolites and steroids (Fig. 27) in which an oxygen atom is

Fig. 27

inserted into an unactivated C-H bond.<sup>114</sup> Cytochrome P-450 has also been found to be involved in heme cleavage and hemoglobin catabolism.<sup>115</sup> This process is analogous to a similar heme cleavage that occurs in the myoglobin system.<sup>116</sup> These extremely complex systems may be better understood through the use of simpler synthetic metalloporphyrin model systems.

The nature of the interaction of molecular oxygen and iron in hemoproteins is the key to understanding many biological processes. Myoglobin, an oxygen carrying protein, consists of a 153 residue peptide and an iron(II) protoporphyrin IX complex. Collman and co-workers<sup>117</sup> have prepared and characterized crystalline iron(II) porphyrin-dioxygen complexes which serve as oxymyoglobin models. "Picket-fence porphyrins" (vide supra) (Fig. 25) were developed to stabilize the iron-dioxygen species by shielding the oxygen in an area of low dielectric constant and low acidity. This shielding prevents the oxygen from reacting with another iron porphyrin (irreversible oxidation), while addition of a base on the unhindered side of the "fence" would allow binding of oxygen only within

the "fence" (Fig. 28) and prevent bimolecular reactions. Such a coordination site would closely resemble that formed in a hemoprotein by the

Fig. 28

envelopment of the peptide residue.

These model compounds bind oxygen reversibly in an end-on, angular fashion, (orientation II, Fig. 26) with possible multiple bond character in the Fe-O bond. The importance of these model compounds to an understanding of the nature of oxygen-carrying natural products cannot be overstated. They clearly provide a model system which allows a study of such factors as possible H-bonding to dioxygen, the influence of the trans axial ligand and the reduction potential of dioxygen complexes--all factors which are crucial to a more complete understanding of complex oxygenases such as cytochrome P-450.

#### Summary

We have presented in this article a very brief introduction to a fascinating class of compounds which are of great interest and importance to people in many different fields. An understanding of the nature and reactions of synthetic porphyrins and metalloporphyrins is vital to man's efforts to solve pressing problems of medical, industrial, and theoretical considerations.

Great strides have been made in this field in recent years. Much advancement has been made possible through the development of powerful new synthetic techniques for both porphyrins and metalloporphyrins.

The preparation and study of these synthetic species is an area of continuing interest to a multitude of diverse interests, all connected by the porphyrin ring!



TABLE I  
Some Biological Compounds Containing  
Porphyrin-like Ligands

Compound	Metal	Compound	Metal
Hemoglobin	Fe	Peroxidase	Fe
Myoglobin	Fe	Oxidase	Fe
Cytochrome	Fe	Cobalamin (Vitamin B <sub>12</sub> )	Co
Catalase	Fe	Chlorophyll	Mg

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118. We thank the Office of Naval Research for support of this work. We also thank our colleagues cited in various references for their contributions.

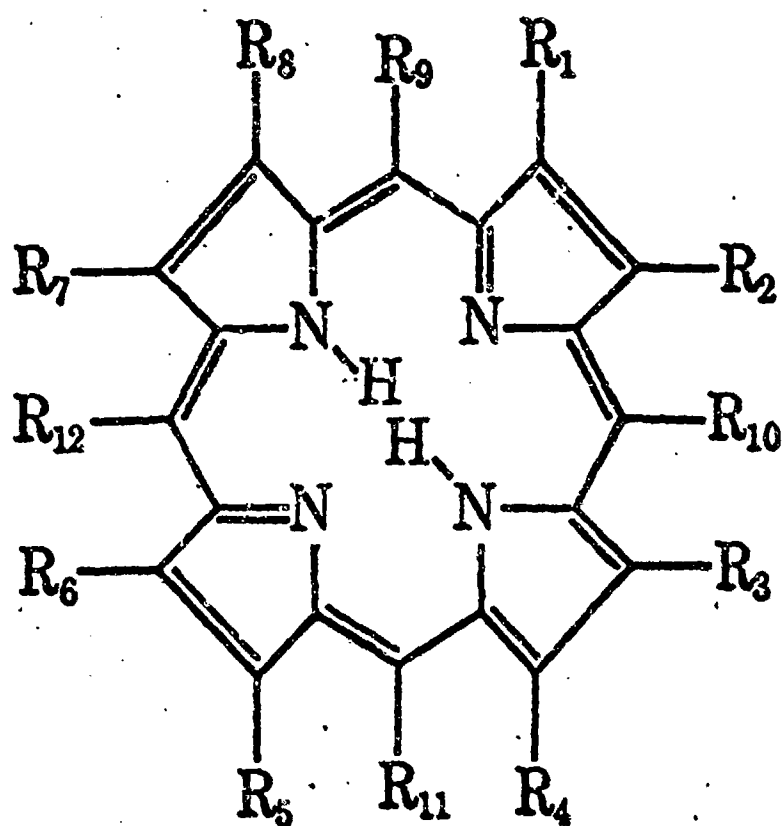


Fig. 1. Porphine, the tetrapyrrole parent compound.

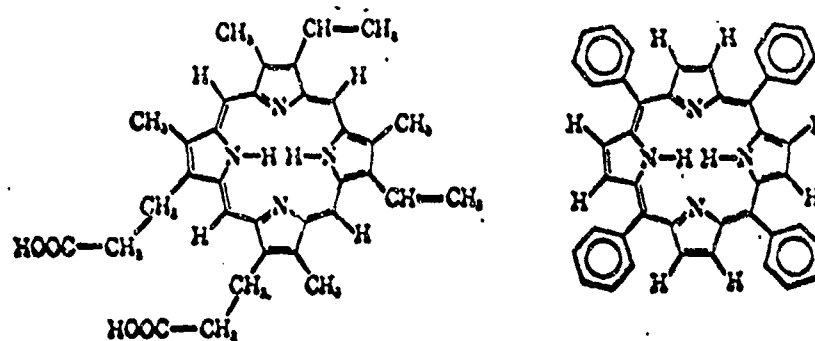


Fig. 2. Protoporphyrin IX, a "natural" porphyrin and meso-tetraphenylporphine, a synthetic porphyrin.

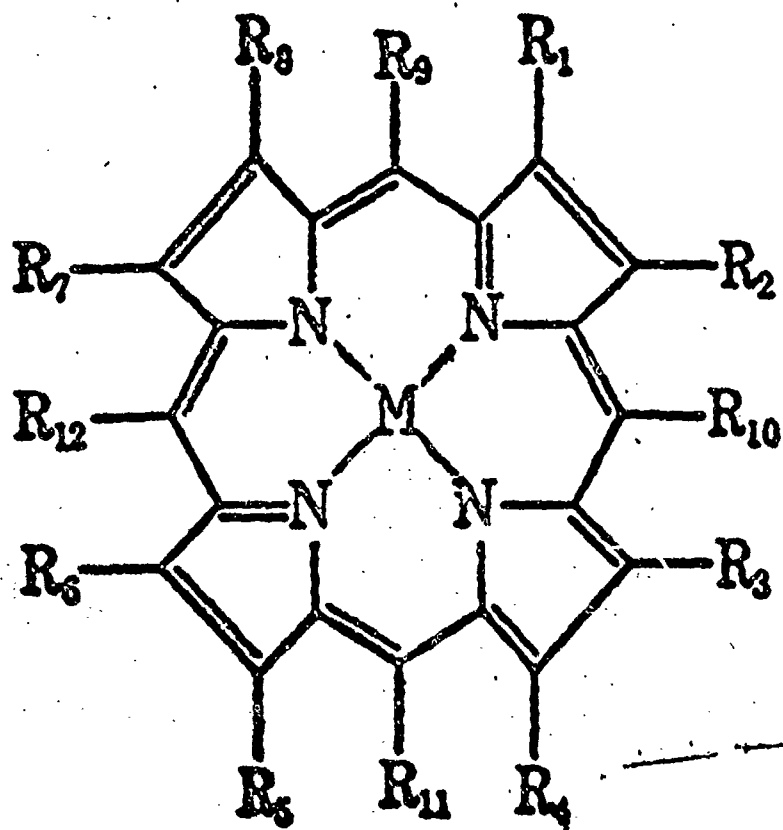


Fig. 3. Metalloporphyrin (general formula).

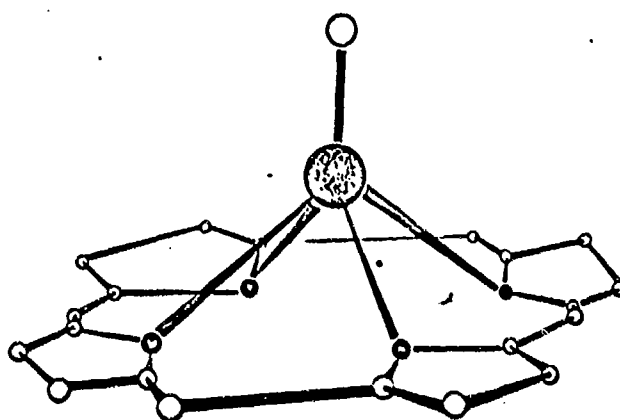


Fig. 4. An out-of-plane metalloporphyrin.

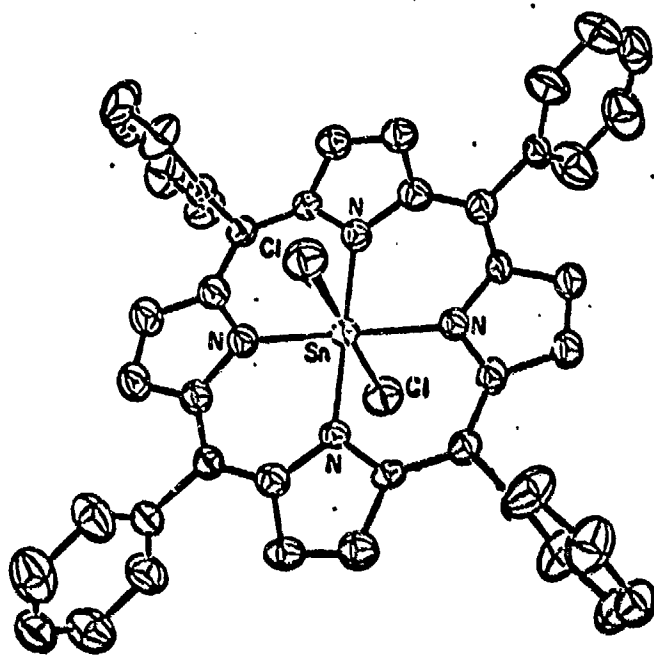


Fig. 5. Dichlorotetraphenylporphinatotin(IV),  
 $(\text{Cl})_2 \text{Sn}(\text{TPP})$

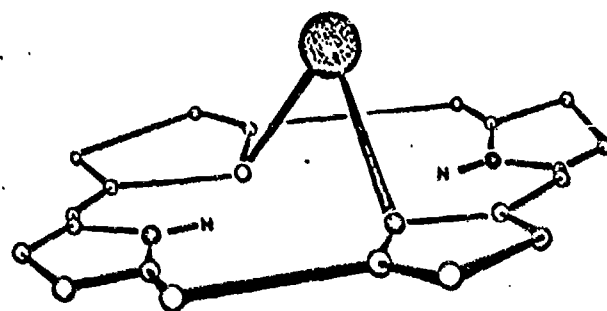


Fig. 6. The "sitting-atop" (SAT) complex.

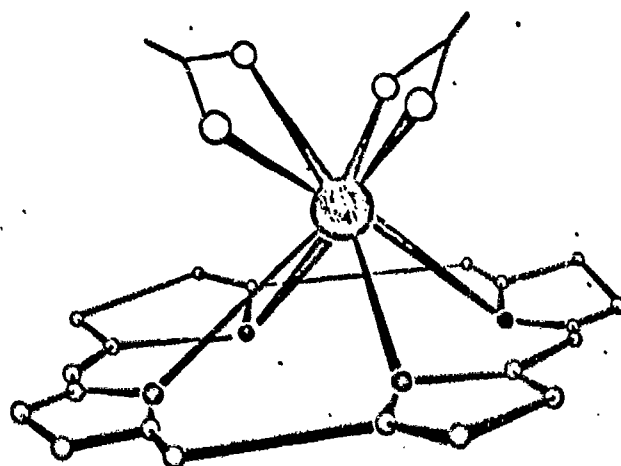


Fig. 7

Fig. 7. Proposed structure of  $\text{Zr(IV)}$  (OEP) and  $\text{Hf(IV)}$  (OEP).



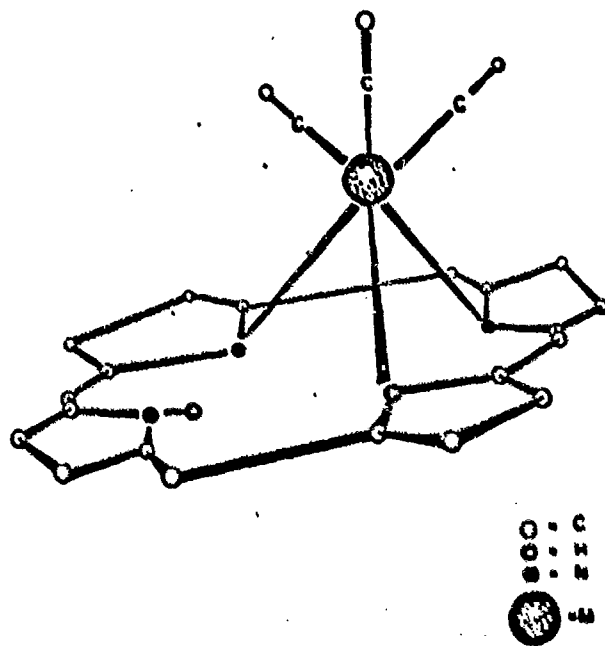


Fig. 8. Structure of the (H-HP)  $\text{Ni}(\text{CO})_3$  complex.

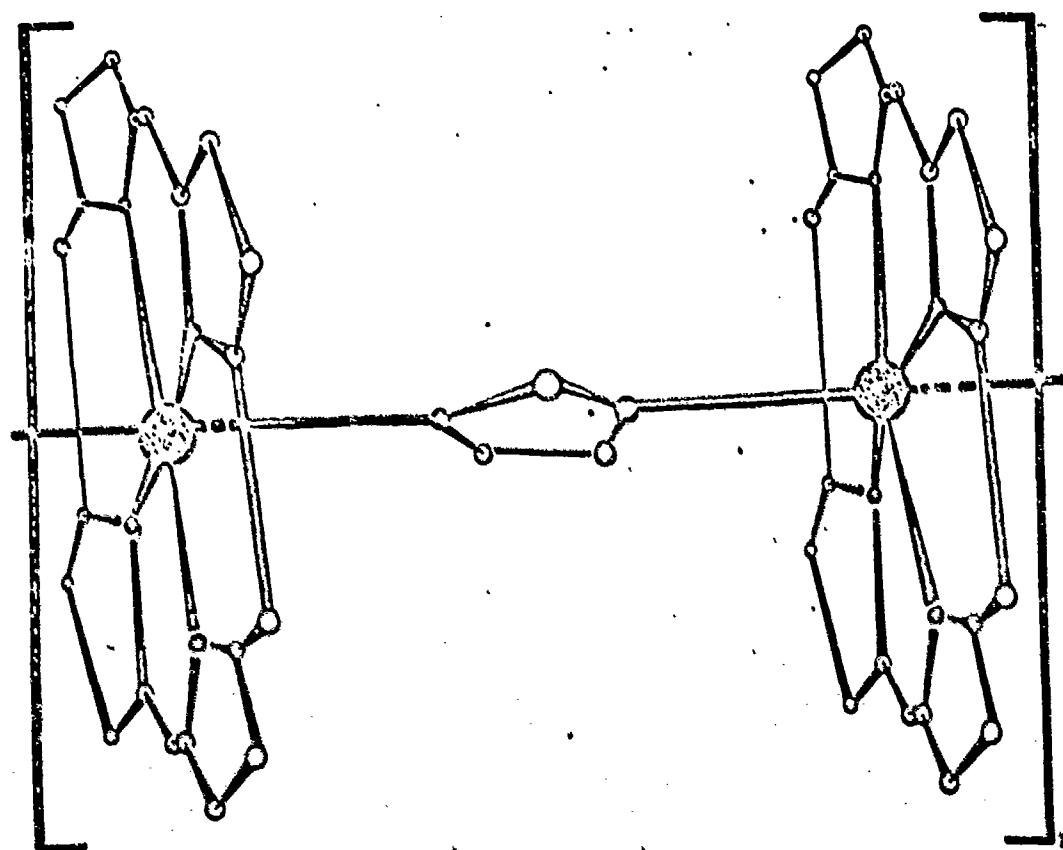


Fig. 9. Structure of the Fe(TPP)-u-imidazolate polymer.

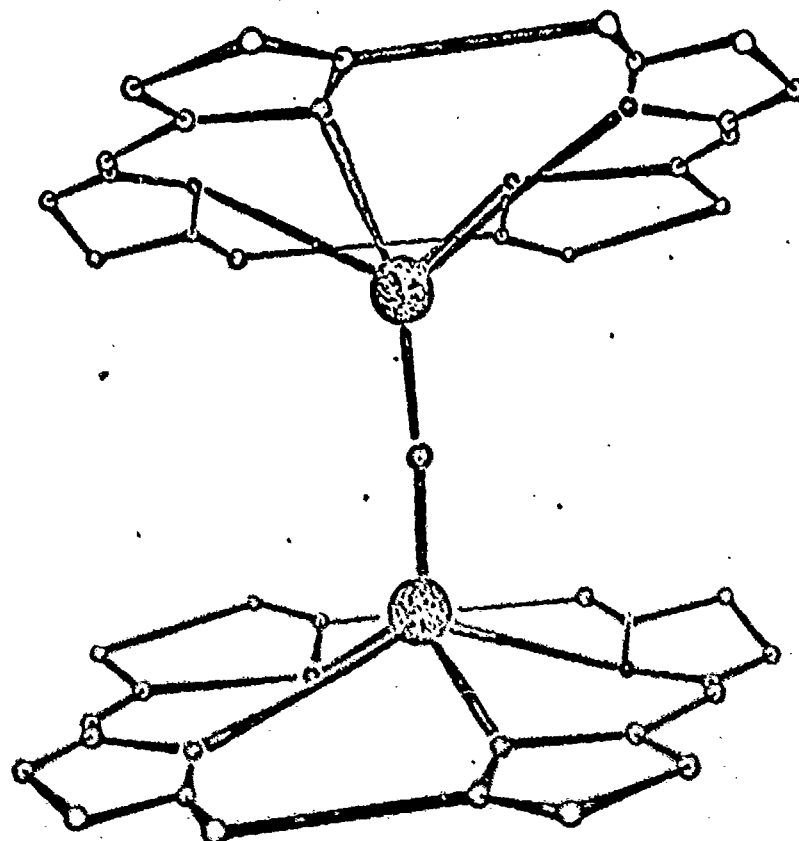


Fig. 10. The oxo-bridged hematin dimer.

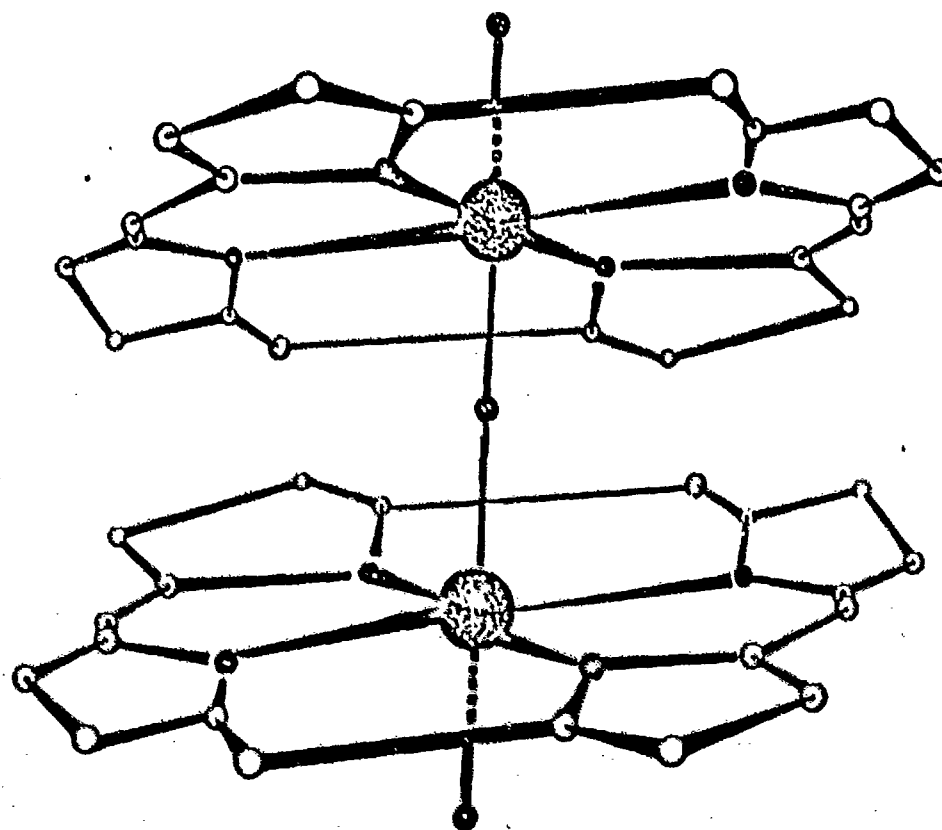


Fig. 11. Structure of the u-oxo-[(Por) M=O]<sub>2</sub> complex

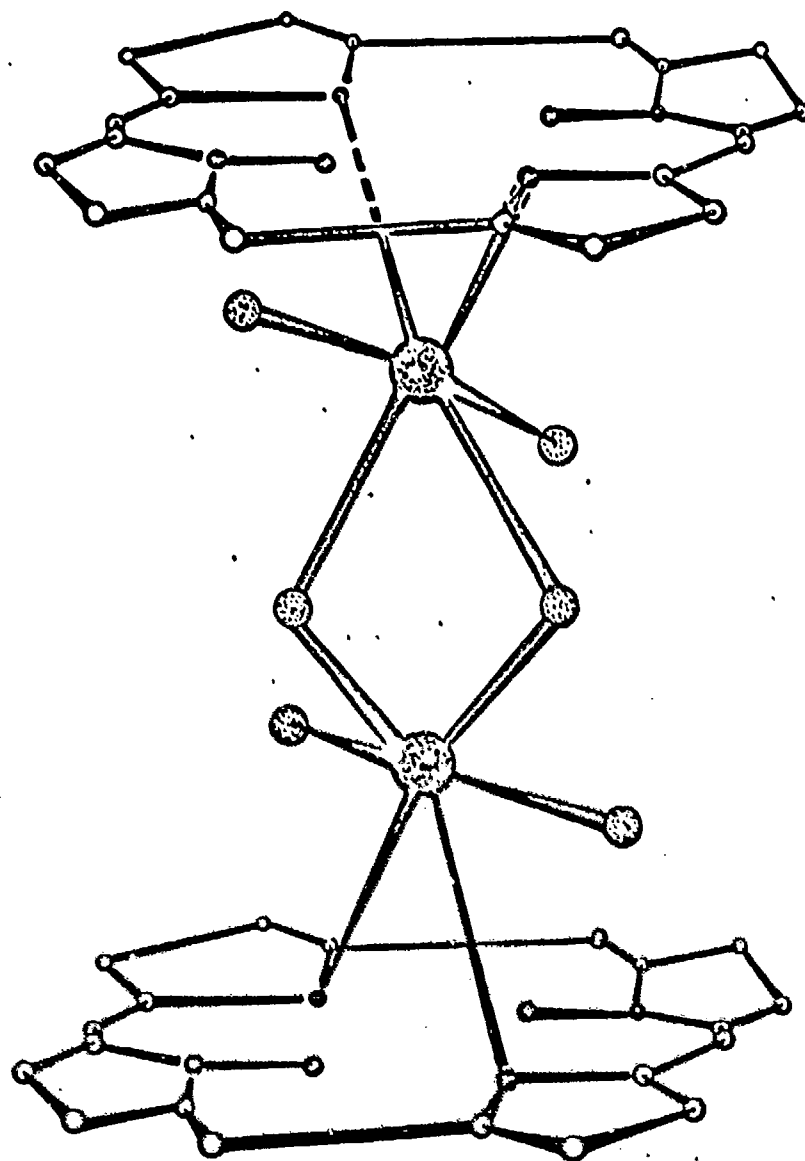


Fig. 12. Proposed "sitting-atop" structure for the dinuclear dimetallic iron porphyrin intermediate.

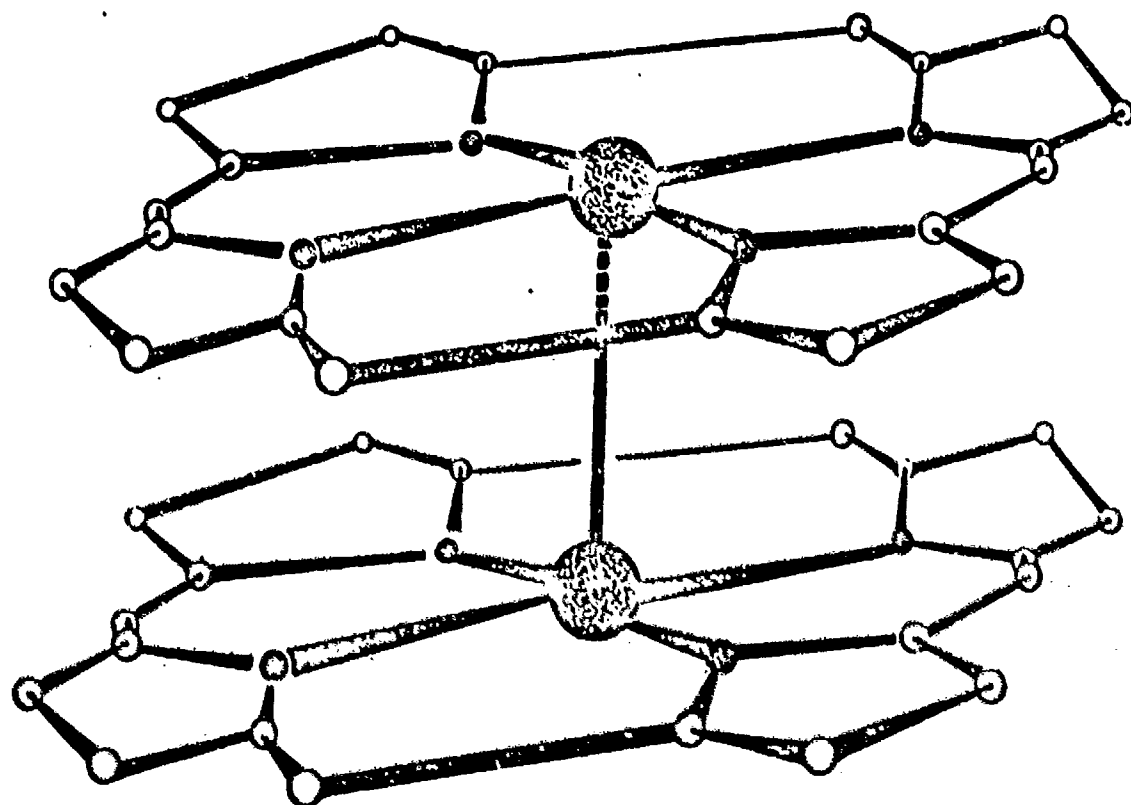


Fig. 13. Structure of the proposed ruthenium porphyrin dimer.

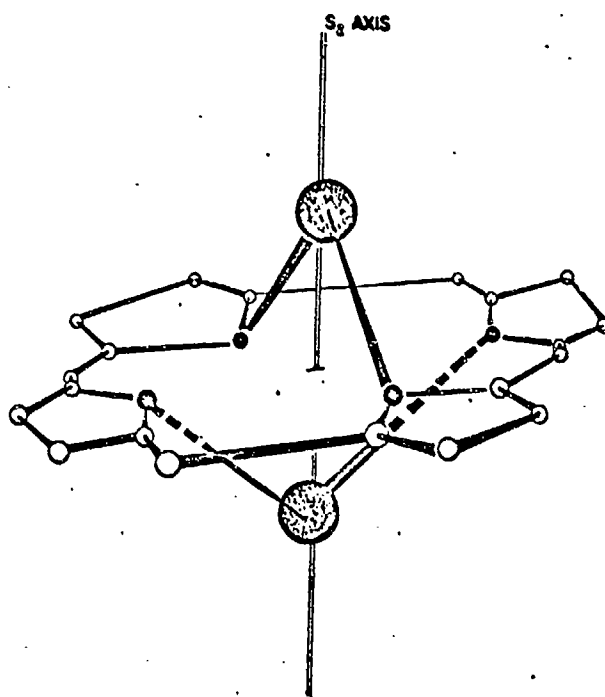


Fig. 14. Proposed model for mononuclear dimetallic porphyrin complexes.

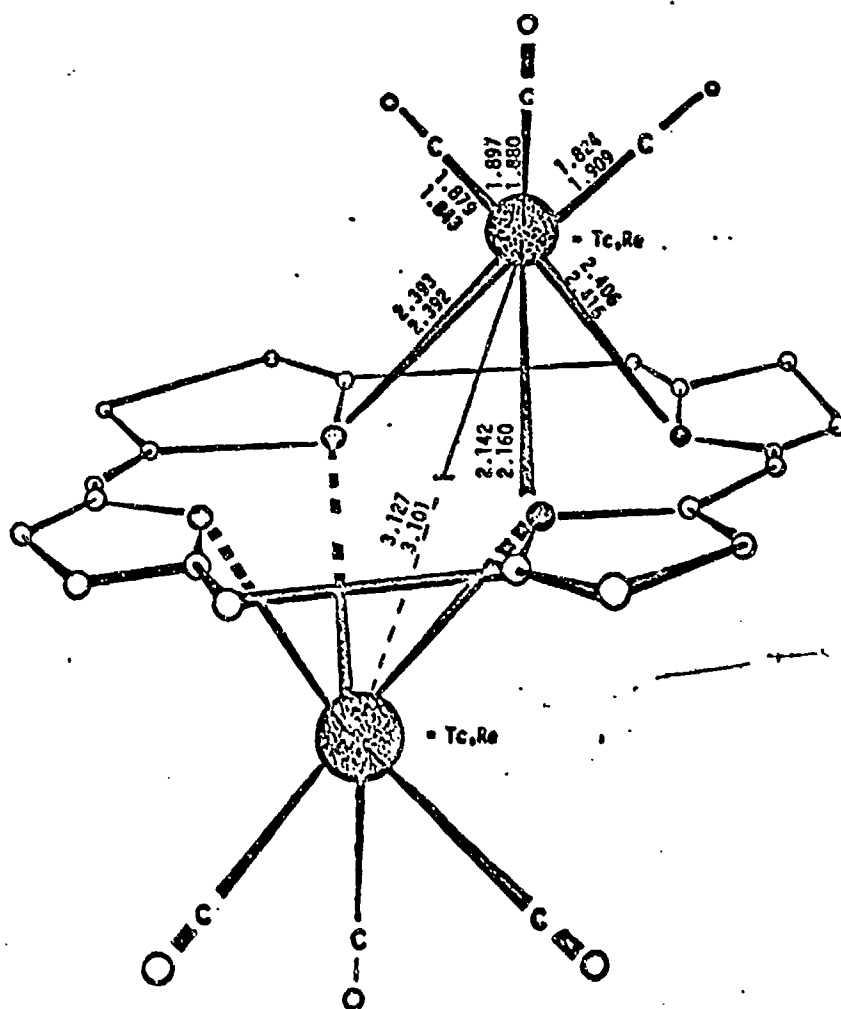


Fig. 15. Coordination sphere about the Rhenium atom in the dimetallic species  $(\text{TPP})[\text{Re}(\text{CO})_3]_2$ .



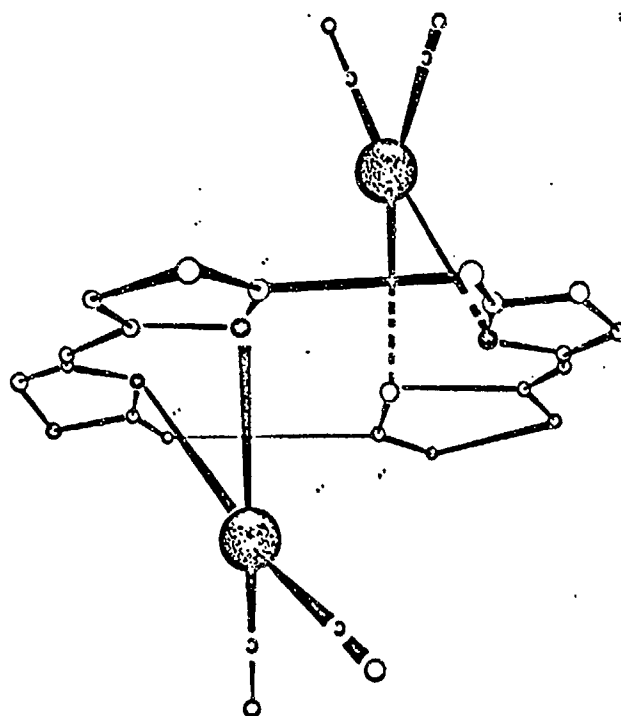


Fig. 16. Structure of  $(\text{OEP})[\text{Rh}(\text{CO})_2]_2$

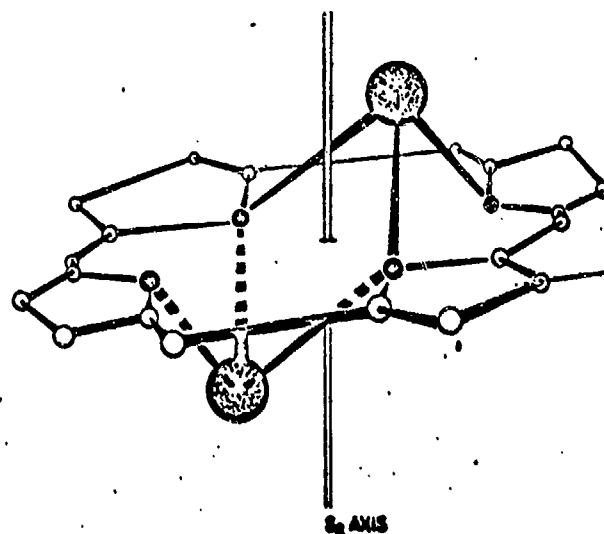


Fig. 17. Proposed new model for mononuclear dimetallic porphyrin complexes.

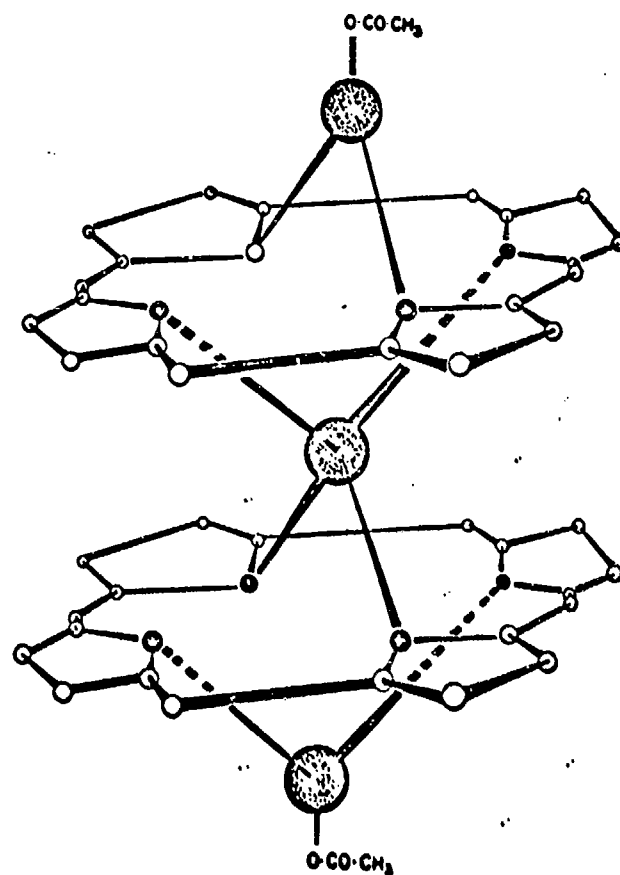


Fig. 18. Proposed structure of the "triple-decker" Mercury porphyrin complex.

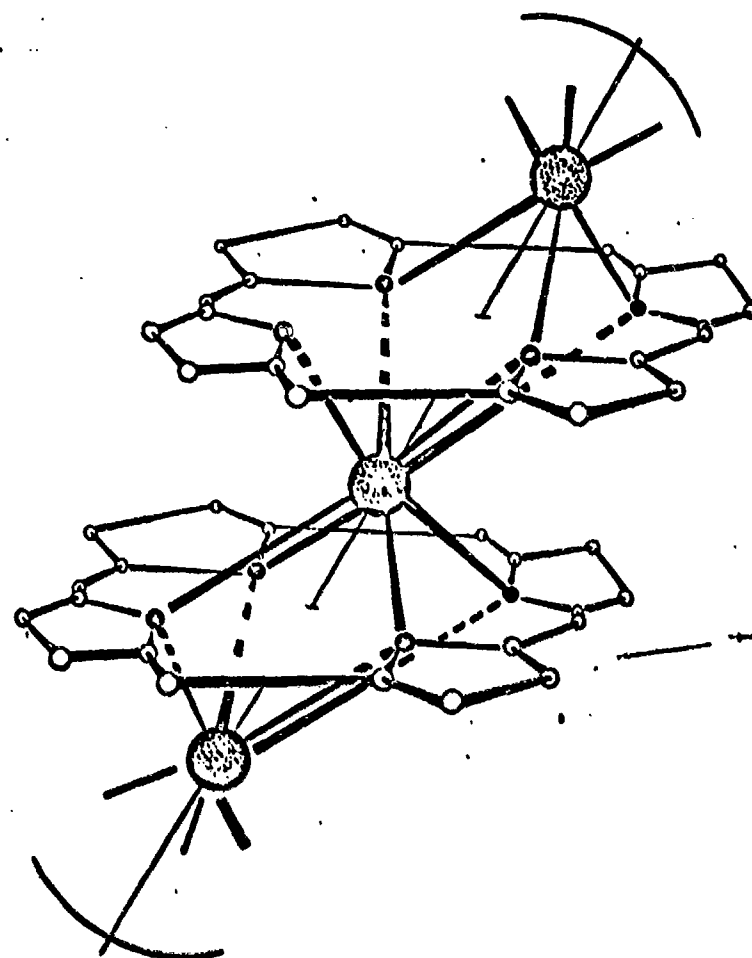


Fig. 19. Proposed structure of a "stacked" porphyrin polymer.

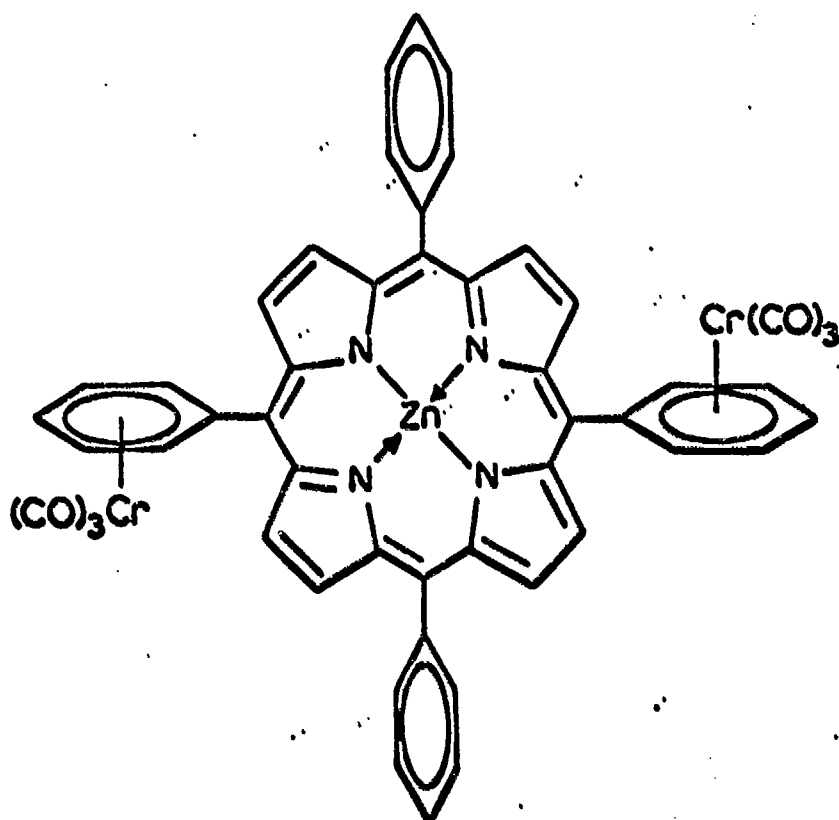


Fig. 20. Structure of bis-( $\eta$ -Cr(CO)<sub>3</sub>)-Zn(TPP).

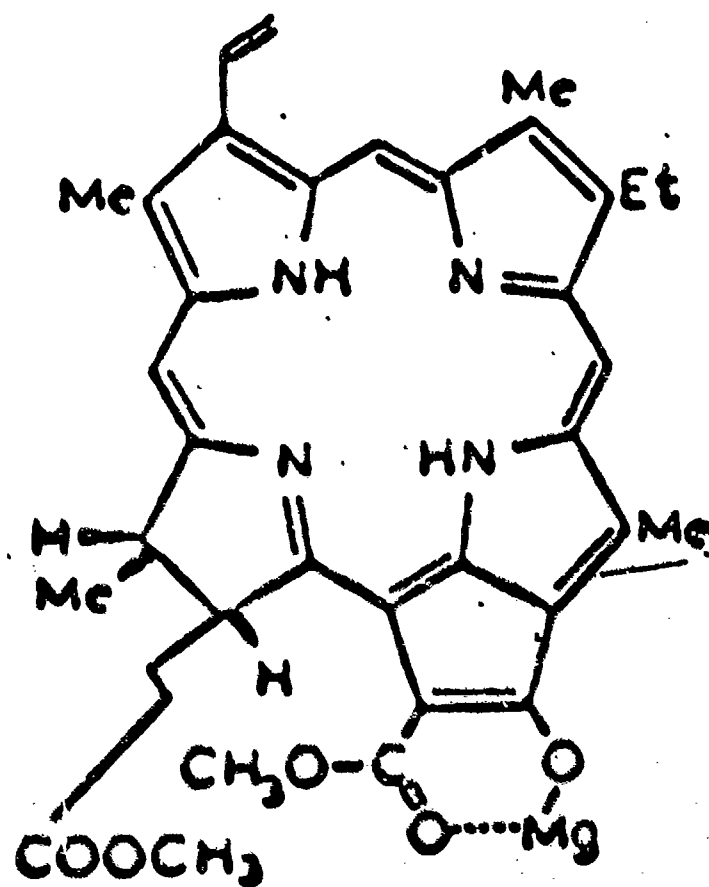


Fig. 21. Structure of a "peripheral complex" in which the metal is associated with substituents on the periphery of the macrocycle.

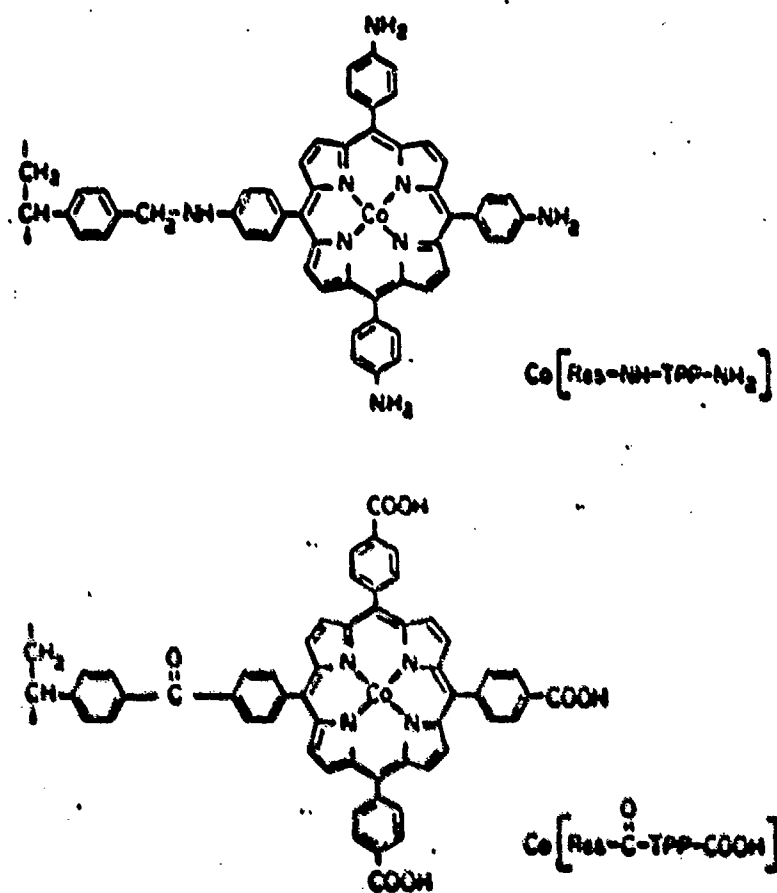


Fig. 22. Polymer-bonded metalloporphyrin complexes.

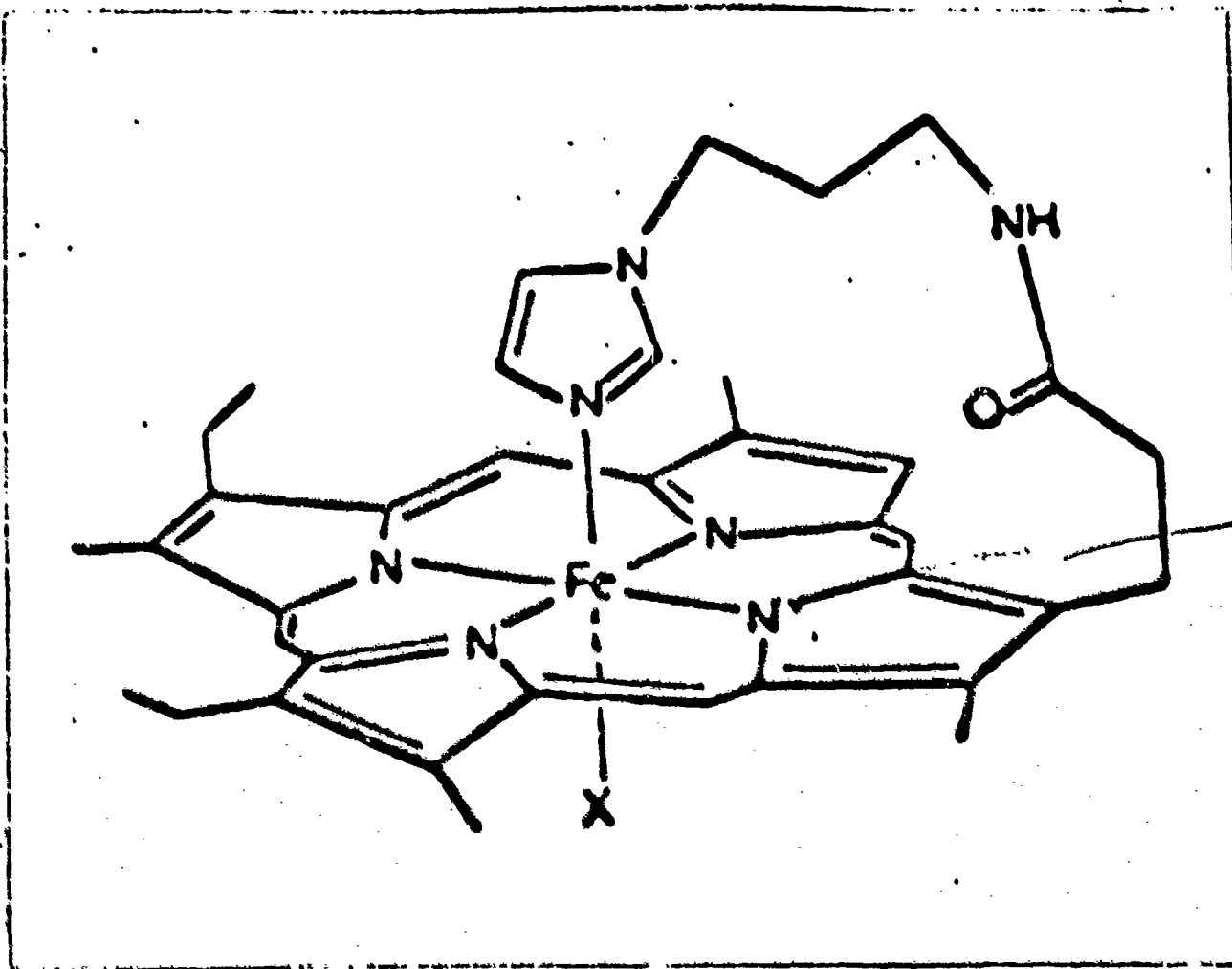
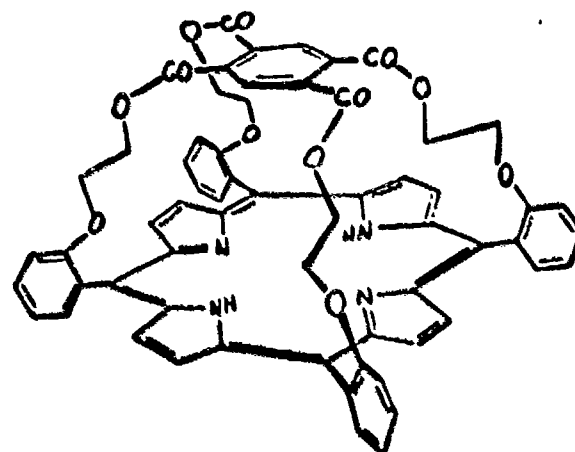
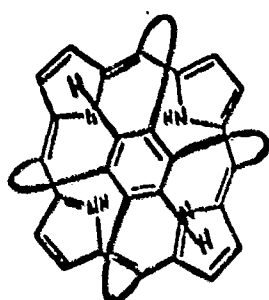


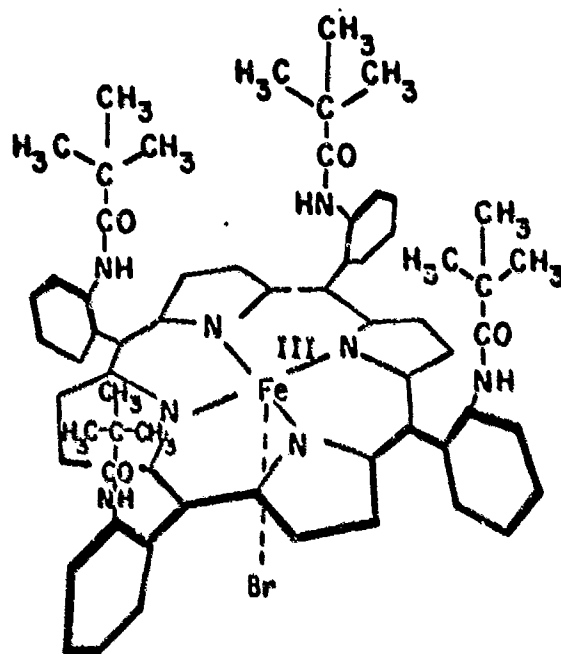
Fig. 23. The "myoglobin model".





"CAPPED"

Fig. 24 Structure of a "capped" or "crown-heme" porphyrin.



FeBr( $\alpha,\alpha,\alpha,\alpha$ -TpivPP)  
"PICKET FENCE"

Fig. 25 Structure of the "picket-fence" metalloporphyrin Fe Br( $\alpha,\alpha,\alpha,\alpha$ -TpivPP).

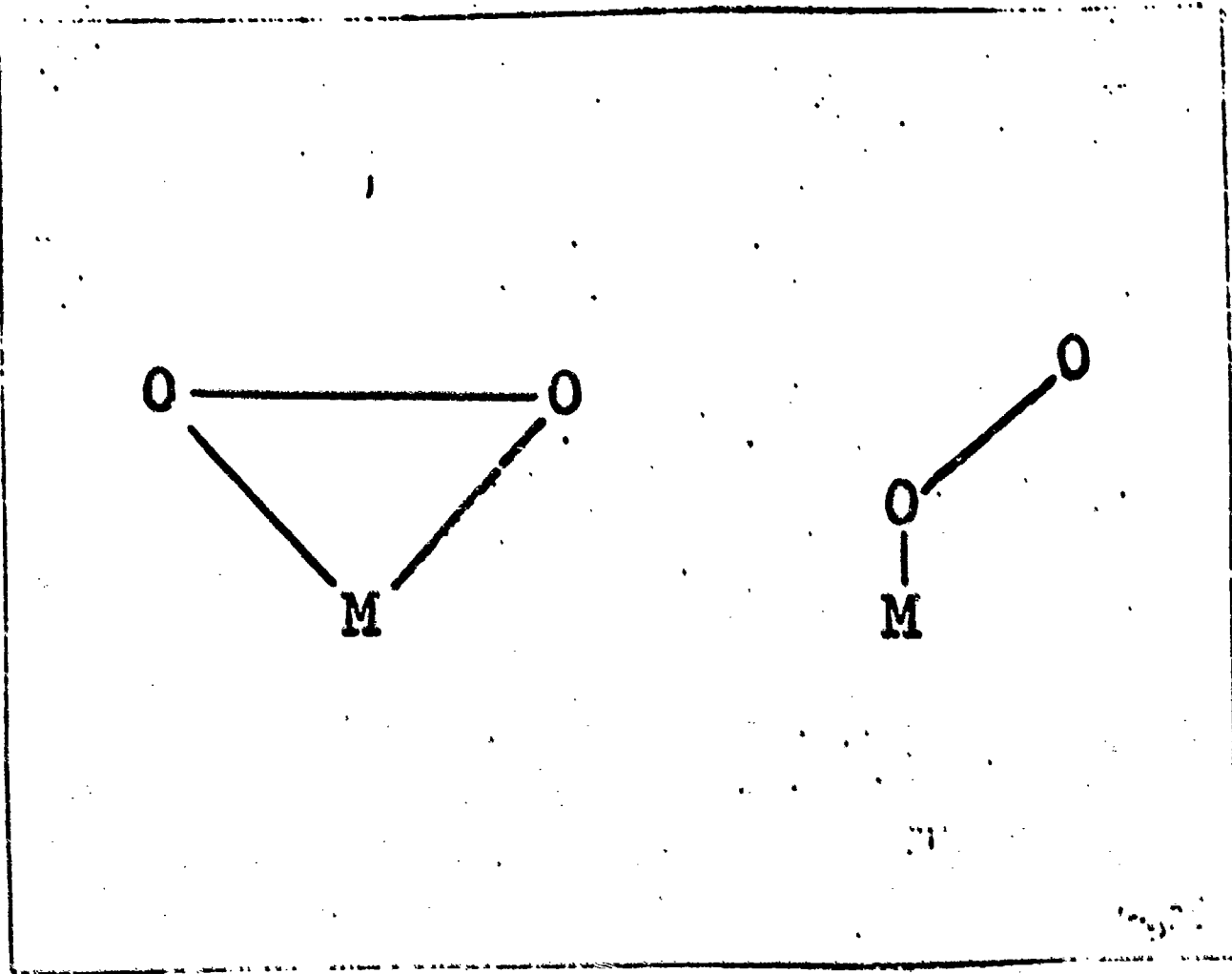


Fig. 26. Possible orientations of a dioxygen-metal complex.

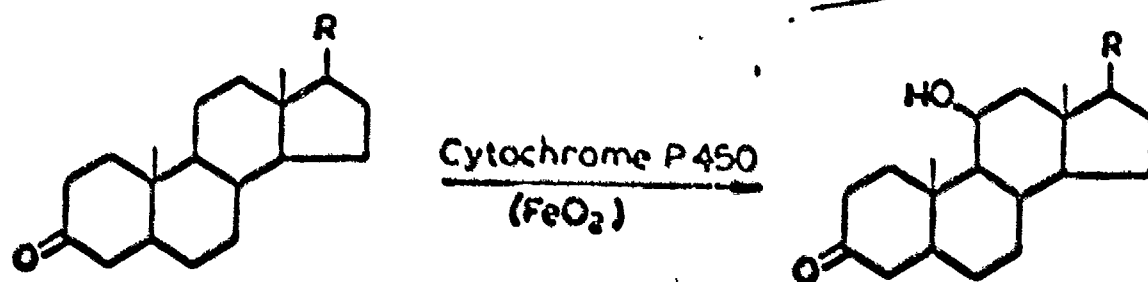


Fig. 27. The hydroxylation-of-a-steroid by cytochrome P-450.

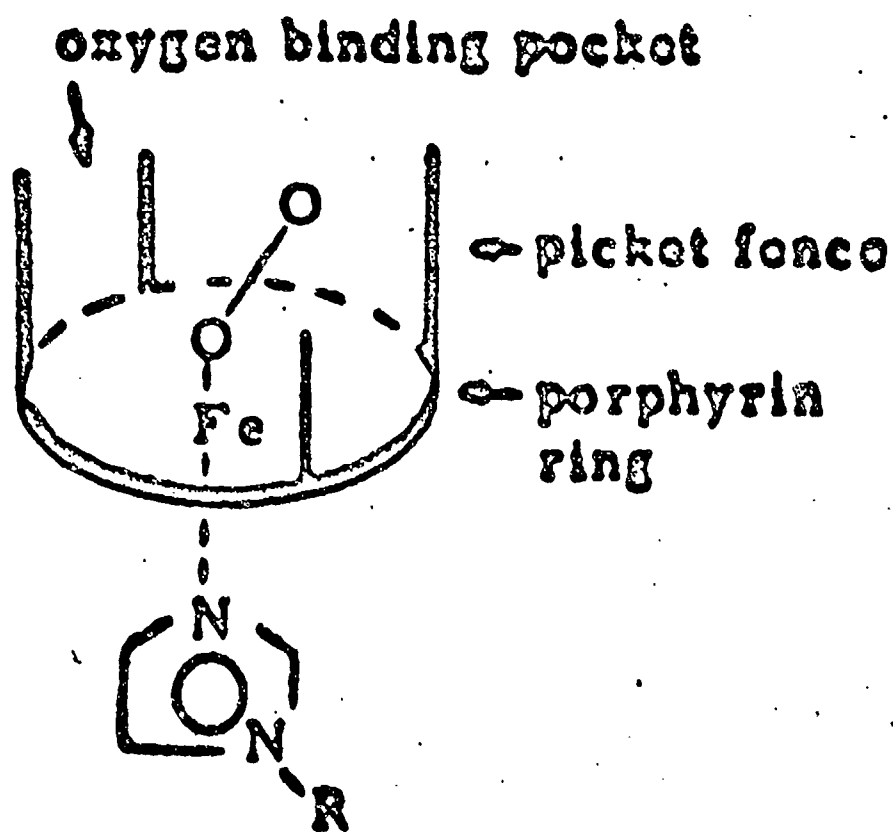


Fig. 28. Schematic representation of the coordination sphere about iron in the oxygen complex of a "picket-fence" porphyrin.